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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/845,352	05/01/2001	Steven L. Stice	P 0280611	3443

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EXAMINER	
CROUCH, DEBORAH	
ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 08/06/2002

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/845,352	STICE ET AL.	
	Examiner	Art Unit	
	Deborah Crouch	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 June 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-55* is/are pending in the application.

4a) Of the above claim(s) *7-14,26-32 and 36-46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,15-25,33-35 and 47-55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Claims 1-55 are pending.

Applicant's election without traverse of Group I, claims 1-6, 15-25, 33-35 and 47-55, in Paper No. 4 is acknowledged. Claims 7-14, 26-32 and 36-46 are withdrawn from consideration as they are directed to nonelected subject matter.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6, 15-17, and 47-54 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to methods of treating a patient in need of cell or tissue transplantation comprising administering to or transplanting a fetal dopamine cell or tissue from a cloned ungulate animal or embryo, a method of treating Parkinson's Disease comprising transplanting a therapeutically effective amount of a cloned, transgenic fetal dopamine cell, a method of treating Parkinson's Disease comprising transplanting a therapeutically effective amount of a cloned fetal dopamine neuronal cell where the dopamine cell is isolated from a fetus produced by nuclear transfer of a differentiated donor ungulate cell, a method of using an ungulate fetal dopamine neuronal cell like to treat Parkinson's Disease, wherein the cell line is obtained from a cloned fetus produced by nuclear transfer from a differentiated cell propagated in culture, a method of treating Parkinson's disease comprising inserting a donor ungulate cell or nucleus into an enucleated oocyte, isolating at least one fetal dopamine cell or mesencephalic tissue from at least one fetus, transplanting said dopamine cells or mesencephalic tissue in to the brain of patient.

The elected group is to methods of treating Parkinson's Disease. Therefore all claims are examined for the treatment of Parkinson's Disease, only.

The claims are not enabled because at the time of filing neither the art nor the specification provided guidance that transplanting a cell or tissue from a cloned ungulate into an unrelated species would provide a treatment effect. The specification does not provide guidance for the inhibition of hyperacute rejection of xenogeneic transplanted cells. As for the cloning of ungulates from adult tissues, applicant has only enabled cloning by using a cell that has been expanded in culture, that is, a cell undergoing rapid cell division.

The use of genetically engineered dopamine producing cells has presented problems in that it has been difficult, after transplantation, to obtain permanently high levels of expression of the transgene and alleviate Parkinson's symptoms (Lindvall (1999), page 635, col. 2, lines 1-20). In particular, neural stem cells transfected with a gene for Nurr-1, did not exhibit characteristics of dopamine neurons, even when treated with trophic factors, cytokines, mitogens and other factors known to induce differentiation/growth/ survival of endogenous dopamine neurons. Barinaga sates that, with regards to the implanting of fetal dopamine neural cells to relieve Parkinson's symptoms, that stem cells need to be coaxed into this type cell for implantation, but that this type of development of stem cells is a big challenge (page 1, parag. 1 and 2). Stems cells must be capable of developing into dopamine neurons and be efficient to be as effective as the implants from aborted fetuses (Barinaga, page 1, parag. 2). However, before stem cell therapy for Parkinson's disease can be implemented, researchers must first learn how to keep stem cells dividing for many generations and be able to cause them to develop into the type of neuron needed to treat Parkinson's Disease (Barinaga, page 2, parag. 5).

With regard to cross-species implantation, xeno-rejection is a problem that makes this methodology unpredictable. Lindvall (1999) states that the first attempts to use porcine

xenografts in PD patients, survival of dopamine neurons has been poor and clinical benefits are uncertain (page 635, col. 2, lines 1-5). While autologous transplantation was enabled by the art, xenotransplantation was problematic as the art did not have the means to prevent rejection associated with xenotransplantation. Xenogeneic transplantation is to of two types: discordant, where a hyperacute rejection that involves complement occurs essentially immediately after implantation and concordant, where the rejection process is over many days or months, and is due to antibody reaction. Neither of these types transplantation and their respective rejections have been overcome by treatment modalities that the claims which encompass them are enabled without specific disclosure by the specification. Discordant xenogeneic transplantation is recognized by the art to be the transplantation of tissue from New World Monkeys and other non-primate species into Old World Monkeys and humans (Galili (1994), page 84, col. 3, parag. 3, lines 3-9). Ryan (1995) stated that transplantation between distantly related species such as pig, and by analogy bovine, and human results in irreversible graft loss due to hyperacute rejection (page 967, col. 1, parag. 1, lines 4-9). Ryan further discusses transgenic pigs expressing human DAF or CD59 as a potential means for overcoming xenograft rejection (page 967, col. 1-2, bridg. parag.). In 1997, Lanza et al. provided encouraging words on the use of pig organs and cells for treatment of human diseases, but indicated that such transplantation was not at that time a viable solution to the problem of human organ failure (page 59, col. 1, parag. 3). The specification does not provide any additional guidance or teachings as to the means to overcome discordant xenogeneic transplantation by either by co-therapies, or by altering the genome of the donor ungulate to inhibit or prevent the massive hyperacute rejection observed in such transplantation. Thus these teachings in the art at the time of filing clearly teach that discordant xenotransplantation was unpredictable. Thus the skilled artisan would have had to engage in an undue amount of experimentation to implement the

xenotransplantation of differentiated cells produced by applicant's method. Immuno-suppression does not affect xeno-rejection (Mandel, page 155). There is further evidence that the implantation of tissue into immune privilege sites provides some but not efficient protection to xenografts. As the brain is considered an immune privilege site, xenorejection still proposes a problem for the cross-species transplantation of cells and tissues to treat Parkinson's Disease.

The specification in providing guidance does not provide teachings for the in vitro development of embryonic stem cells into dopamine neuronal cells. Further, there are no teachings in the specification of methods to overcome xenograft rejection when cross-species transplantation of cells and tissues takes place. Without such guidance, and in view of the teachings in the art at the time of filing, the skilled artisan would need to engage in an undue amount of experimentation without a predictable degree of success to implement the invention as claimed. The only examples involves the removal of mesencephalic tissue from a cloned bovine fetus (specification, page 114-119) and the implantation of such tissue into a rat model for Parkinson's disease. However, the effects on rotation were lost after two months. It is not clear that a two month correction of a Parkinsonian symptom has a benefit to the patient. Further, as stated in the art citations above, porcine grafts die prior to giving any benefit to humans. Thus it is unpredictable that bovine tissue will be functional in humans. Further, the specification provides no correlatable guidance to the expression of a DNA sequence in embryonic stem cells or fetal dopamine cells that relate to the treatment of a disease or condition. The only DNA sequence expressed is a marker gene which demonstrates the engrafted bovine fetal dopamine cells.

The question is raised with regard to the enablement of the claims in view of the above cited art as to why an artisan would want to merely treat, but not have a therapeutic

outcome? The specification does not provide any guidance on this, as it only discloses the claimed methods as providing a therapy.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 18-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 18-25 are confusing as what is meant by a cloned cell line grown and maintained in a cloned bovine. Cell lines in the art are in vitro culture of a single cell type.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 18-25 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Sims et al (1993) Proceed. Natl. Acad. Sci. 90, 6143-6147 .

Sims teaches a cloned bovine genetically identical to a prior existing bovine, where the cloned bovine comprises a clone cell line, where the bovine is demonstrated to be an embryo, a blastocyst, fetal and adult, where the cell line is both totipotent and differentiated, where the cell line comprises differentiated dopamine neurons, somatic and germ cells, as the cloned bovine of Sims inherently contains these cell types (page 6146, col. 1, parag. 1 and 2).Thus Sims, clearly anticipates the claimed invention.

Claims 33-35 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Huffaker et al (1989) Exp. Brain Res. 77, 329-336.

Huffaker teaches a cell suspension produced from fetal pig ventral mesencephalic tissue (page 330, col. 2, parag. 2). Thus Huffaker clearly anticipates the claimed invention.

> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 33-35 and 55 are rejected under 35 U.S.C. 102(e) as being clearly anticipated by U.S. Patent 6,294,383 B1 issued September 25, 2001 (Isacson).

Isacson teaches pig mesencepahlon cells that have been genetically modified by an insertion of a DNA sequence to express a foreign molecule (col. 18, line 66 to col. 19, line 10 and col. 22, lines 34-39). Thus Isacson clearly anticipates the claimed invention.

Claims 1-6, 15-17, and 47-54 are free of the art. At the time of filing the prior did not teach methods of treating Parkinson's disease, methods of using a fetal dopamine neuronal cell for transplantation purposes to treat a patient with Parkinson's disease where the at least one cell or tissue is obtained from a cloned ungulate animal or embryo made by nuclear transfer using a differentiated cell that had been propagated in culture.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Crouch, Ph.D. whose telephone number is 703-308-1126. The examiner can normally be reached on M-Th, 8:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0916.

Deborah Crouch

Deborah Crouch, Ph.D.
Primary Examiner
Art Unit 1632

dc
July 30, 2002